

**REMARKS**

This paper is filed in response to the Office Action dated December 11, 2008. Claims 1 and 57-69 are currently under examination. Claims 2-13, 17, 22, 26-28, 30, 33-39, 43-44, 52, and 57-69 have been withdrawn. Claims 14-16, 18-21, 23-25, 29, 31-32, 40-42, 45-51, 53-56, 71-74, 76, 78, 84-87, 89, and 92-93 have been cancelled.

Applicant has amended the specification herein to properly characterize Trademarked goods, *i.e.*, to capitalize the mark, and, where appropriate, the mark has been accompanied by the generic term.

Applicant also presents herewith an Abstract, on a separate sheet, to be included in the application.

Claim 1 has been amended herein to recite:

1. A method for determining the likely outcome of treatment or the need of treatment for a subject having a disease or disorder, undergoing treatment for a disease or disorder, having had a disease or disorder, or having received treatment for a disease or disorder, said disease or disorder being associated with Factor XIIa, the method comprising:
  - obtaining a sample from said subject,
  - detecting one or more forms of *in vivo* activated Factor XIIa in said sample, which one or more forms includes at least cellular Factor XIIa,
  - wherein said detection of one or more forms of *in vivo* activated Factor XIIa is correlated with at least one state in the development of said disease or disorder.

Support for the amendment can be found throughout the specification. More specifically, the following chart shows each claim recitation and where specific support can be found in the specification.

<b>Claim 1 term</b>	<b>Support</b>
A method for <del>detecting or</del> determining the likely outcome of treatment or the need of treatment for a subject having a disease or disorder, undergoing treatment for a disease or disorder, having had a disease or disorder, or having received treatment for a disease or disorder, said disease or disorder being associated with Factor XIIa, the method comprising:	Pages 4-6
-- obtaining a sample from said subject,	Pages 34-35

<p>-- <u>detecting</u> one or more forms of <i>in vivo</i> activated Factor XIIa in [[a]] <u>said</u> sample, which <u>one or more forms includes at least cellular Factor XIIa</u>, <del>comprises carrying out a procedure that is capable of detecting or determining the form or forms of Factor XIIa under investigation in preference to other forms of Factor XIIa</del></p>	<p>Pages 23-24 (discovery of cellular Factor XIIa)  Pages 46-48 (detection of cellular Factor XIIa)  Page 40-50 (detection of forms of Factor XIIa)</p>
<p><u>wherein said detection of one or more forms of <i>in vivo</i> activated Factor XIIa is correlated with at least one state in the development of said disease or disorder.</u></p>	<p>Pages 4-6  Pages 59-74  Examples 1-21</p>

Additionally, Claims 57, 59-63, and 66 have been amended herein to comply with proper Markush practice form, as request by the Examiner. Support for the amendments is apparent from the original claims. No new matter is presented.

**Response to issues presented under 35 U.S.C. §112, second paragraph**

In the Office Action, Claims 1 and 57-69 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner contends the method of Claim 1 does not set forth any method steps. Further, the Examiner objects to Claim 1 because it allegedly unclear how the method detects forms of Factor XIIa in preference to other forms of Factor XIIa.

As noted above, Applicant has amended Claim 1 to recite:

1. A method for determining the likely outcome of treatment or the need of treatment for a subject having a disease or disorder, undergoing treatment for a disease or disorder, having had a disease or disorder, or having received treatment for a disease or disorder, said disease or disorder being associated with Factor XIIa, the method comprising:
  - obtaining a sample from said subject,
  - detecting one or more forms of *in vivo* activated Factor XIIa in said sample, which one or more forms includes at least cellular Factor XIIa,

wherein said detection of one or more forms of *in vivo* activated Factor XIIa is correlated with at least one state in the development of said disease or disorder.

Most notably, the claim as amended presents clear method steps, *e.g.*, obtaining, detecting, etc., and specifies that the one or more forms of *in vivo* activated Factor XIIa detected includes at least cellular Factor XIIa. Applicant submits that Claim 1, as amended, is in proper form and does not present any issues under 35 U.S.C. §112, second paragraph. Support for the amendment can be found throughout the specification and as further discussed in the chart above.

Further, Claims 57, 59-63, and 66 have been amended herein to comply with proper Markush practice form, as request by the Examiner.

Reconsideration and removal of the rejection of Claims 1, 57, 59-63, and 66 under 35 U.S.C. §112, second paragraph, are respectfully requested.

### **Response to issues presented under 35 U.S.C. §102**

Claims 1 and 57-63 are rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,500,349 to Michael Esnouf (hereinafter "Esnouf"). Specifically, the Examiner contends that Esnouf teaches methods for measuring:

"factor  $\beta$ XIIa via antibodies that show no substantial binding to factor XII. Esnouf utilizes the same antibodies that are disclosed by the instant specification for differential factor XIIa detections (antibodies 2/215, 201/9, 20216.1.9). For example, see page 13 of the disclosure. The detected Factor XIIa is taught to be useful in various diseases or disorders." (Office Action, page 7.)

First, Applicant points out that the claims as previously presented required the detection or determination of one or more forms of *in vivo* activated Factor XII (i.e., XIIa) in preference to other forms of XIIa. As noted by the Examiner, Esnouf describes the detection of  $\beta$ XIIa, which antibodies showed no substantial binding to the unactivated zymogen Factor XII. Accordingly, Applicant submits the Esnouf document fails to anticipate the claims as previously presented.

Further, as previously described, Applicant has amended the claims to recite:

"detecting one or more forms of *in vivo* activated Factor XIIa in said sample, **which one or more forms includes at least cellular Factor XIIa.**"

As noted on page 23 of the specification, persons skilled in the art believed that the activation of Factor XII to Factor XIIa could occur on the surface of cells, notably epithelial cells, through multi-

molecular assemblies involving, e.g., high molecular weight Kininogen, Pre-kallikrein and Factor XII. However, as further described in the specification, it was believed by those skilled in the art that the activated Factor XIIa then dissociated from the cell and did not remain on the cell surface for prolonged periods.

As Applicant discusses in the specification:

"The present invention is based on our surprising observation that Factor XIIa exists in various forms, one of which is Factor XIIa present on the surface of cells circulating in the blood and on remnants thereof and on cellular material derived therefrom. This form of Factor XIIa is called "cellular Factor XIIa". This observation is contrary to the previous findings described above that, after activation in a multi-molecular assembly on a cell surface, Factor XIIa dissociates from the assembly and does not remain bound to the cell." (page 23 of the specification)

A rejection for anticipation under 35 U.S.C. §102(b) requires that each and every feature of the claimed invention be disclosed in a single prior art reference. *See* MPEP §2131. Because Esnouf does not teach or suggest the presence of cellular Factor XIIa for detection, Esnouf fails to anticipate the present claims as a matter of law.

In view of the foregoing, it is clear that the present methods for detecting one or more forms of *in vivo* activated Factor XIIa in said sample, which one or more forms includes at least cellular Factor XIIa, are not taught or suggested by the cited reference. Therefore the rejections under 35 U.S.C. §102(b) must be withdrawn.

### **Response to issues presented under 35 U.S.C. §103**

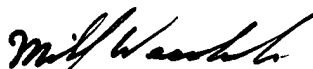
In the Office Action, dependent Claims 64-69 are rejected under 35 U.S.C. §103(a) as unpatentable over Esnouf in view of Coppola et al., *Blood Coagulation & Fibrinolysis*, 7(5): 530-535 (1996) (hereinafter "Coppola"). Specifically, the Examiner notes that Esnouf does not teach the measurement of Factor XIIa in sepsis and disease treatment, but contends that the claims would have been obvious in view of Coppola, which, *inter alia*, teaches that Factor XIIa levels were discovered to be significantly higher in patients with severe sepsis.

However, Coppola does not cure the deficiencies of Esnouf. Neither Esnouf nor Coppola teach or suggest the present methods for detecting one or more forms of *in vivo* activated Factor XIIa in said sample, which one or more forms includes at least cellular Factor XIIa.

For the reasons set forth above, Esnouf or Coppola, alone or in combination, cannot render Claim 1 obvious. Similarly, Claims 57-69, which depend from nonobvious Claim 1, cannot be found obvious under 35 U.S.C. §103 as a matter of law. MPEP §2143.03.

Every effort has been made to advance the case to allowance, to particularly and distinctly define the subject matter of the invention, and to distinguish the invention over the prior art of record. In view of the foregoing remarks, reconsideration and allowance of the claims are respectfully requested.

Respectfully submitted,



Leon R. Yankwich, Reg. No. 30,237  
Michael R. Wesolowski, Reg. No. 50,944  
Attorneys for Applicants  
YANKWICH & ASSOCIATES, P.C.  
201 Broadway  
Cambridge, Massachusetts 02139  
telephone: 617-374-3700  
telecopier: 617-374-0055

**Certificate of Mailing**

The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service under 37 CFR 1.8, postage prepaid, in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below.

June 11, 2009  
date



Margaret Chinappi